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ORIGINAL ARTICLE

Antineutrophil cytoplasmic antibody-associated vasculitis in Taiwan: A hospital-based study with reference to the population-based National Health Insurance database

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Background: Antineutrophil cytoplasmic antibody-associated vasculitis (AAV), including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and Churg—Strauss syndrome (CSS), comprises a group of diseases with significant morbidity and mortality. The incidence and relative frequency of GPA/MPA/CSS are different all over the world. The epidemiology of AAV in Taiwan is still not clear.
Methods: The current study aimed to provide a population-based estimate of the annual incidence of GPA using the Taiwan National Health Insurance (NHI) research database and a single hospital-based estimate of the relative frequency of AAV in Taiwan.
Results: The annual incidence of GPA in Taiwan was 0.37 per million patient-years (95% Poisson rate confidence interval: 0.30—0.45) from 1997 to 2008, according to the NHI database. In our hospital, 24 patients were newly diagnosed with AAV between 2003 and 2011, including eight patients with GPA, 14 with MPA, and two with CSS. The ratio of the number of patients with GPA to that of MPA was 0.57.
Conclusion: The current results provide an estimate of the annual incidence of GPA and the relative frequency of AAV in the Chinese Han community in Taiwan. Such geoepidemiology

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information may help illuminate the interaction between ethnic background and environment in these autoimmune diseases.

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), including granulomatosis with polyangiitis (GPA; previously known as Wegener's granulomatosis), microscopic polyangiitis (MPA), and Churg—Strauss syndrome (CSS), comprises a group of rare diseases associated with high morbidity and mortality. The timely diagnosis of any of these conditions is difficult due to their rare occurrence and variable clinical manifestations. The clinical diagnosis of AAV is facilitated by the recent availability of an enzyme-linked immunosorbent assay (ELISA) for ANCA, which has provided improved specificity compared with an indirect immunofluorescence assay.[1—3] The reported incidence of GPA, MPA, and CSS varies significantly all over the world. A north-to-south gradient of the GPA/MPA ratio is believed to exist according to the European data. For example, the incidence ratio of GPA/MPA is increased in Norway [incidence of GPA and MPA: 10.5 per million and 2.7 per million, respectively (ratio 3.9)] and decreased in Spain [incidence of GPA and MPA: 4.9 per million and 11.6 per million, respectively (ratio 0.42)].[4] Non-Caucasian epidemiological studies of AAV remain limited; a study in Japan showed that MPA comprises up to 83% of AAV.[5] Therefore, an examination of the incidence of AAV across ethnicities and geographic regions in Taiwan may help reveal the interaction between genetic and environmental components as contributing factors to these complex diseases.

There is a paucity of research examining AAV in Taiwan.[6,7] The Taiwan National Health Insurance (NHI), a single health insurance provider for citizens of Taiwan since 1995, is a good data source for the epidemiologic study of these rare diseases. The NHI Research Database uses the Ninth Revision of the International Classification of Diseases (ICD-9) for disease registry. At the time of data collection, only GPA had an ICD-9 code and data on the incidence of MPA or CSS were not available in the NHI database. The incidence of MPA or CSS may be estimated from the relative frequency of GPA, MPA, and CSS. This study aimed to estimate the incidence of GPA using the Taiwan NHI database analysis and to derive the relative incidence of AAV (GPA/MPA/CSS) as well as the clinical characteristics of these patients from a single-center experience.

Methods

National Health Insurance Research Database

The total number of patients with GPA and the annual incidence rate were derived from the NHI Research Database. In 2008, the NHI provided coverage for a population of nearly 23 million (approximately 99.5% of the population). The NHI research database includes all claim information of outpatients, inpatients, and emergency departments.[8] GPA (ICD-9 446.4) and end-stage renal disease (ESRD; ICD-9 585) that require renal replacement therapy are listed as catastrophic diseases in the NHI database. Patients with these severe diseases are exempt from a copayment at the time of care. In addition, the catastrophic disease registry is under the regulation of the NHI authority.

For the current study, the catastrophic illness file of the NHI claims data was used for analysis. We selected the patients who were diagnosed with GPA (ICD-9 446.4) between 1997 and 2008. The incident date was defined by the date of catastrophic illness certification. The annual incidence rate was defined as the number of new cases divided by the number of person-years observed during a given time period. Sex and age at diagnosis were obtained. The number of patients with ESRD and GPA, and the time interval between the diagnosis of ESRD and GPA were also calculated.

Generation of patient lists in the hospital-based study

Between October 2003 and October 2011, a list of patients diagnosed with AAV was generated from computerized databases of serology, pathology, electronic chart record system, and consultation records in the Far Eastern Memorial Hospital, New Taipei City, Taiwan. Patients with a creatinine clearance of less than 15 mL/minute were classified as having ESRD. All study protocols were approved by the Institutional Review Board of the Far Eastern Memorial Hospital (FEMH-IRB-100165-E).

Case ascertainment and classification

Complete chart reviews revealed patient demographic data, including sex, age at diagnosis, initial presentations, ANCA status, treatment, and prognosis. Clinical records of surrogate markers such as sinusitis, image studies of lung, urine analysis, and pathology reports were reviewed carefully. Proteinase 3 ANCA (PR3-ANCA) and myeloperoxidase ANCA (MPO-ANCA) were tested using commercial ELISA kits (EliA PR3 and EliA MPO; Phadia AB, Uppsala, Sweden). We followed the European Medicines Agency (EMEA) algorithm to avoid overlapping of cases and to ensure consistency of classification across studies.[9]

Statistical analysis

The annual incidences of GPA in each 3-year interval between 1997 and 2008 were calculated. The 95% confidence intervals of Poisson rate were calculated for each period using StatsDirect Version 2.7.9 (StatsDirect Ltd, Altrincham, UK).

Results

GPA in the NHI research database

A total of 96 patients with GPA were identified using the NHI database between 1997 and 2008. The distribution of patient age and sex is shown in Table 1. The average patient age was 49.72 ± 16.27 years (males: 47.30 ± 14.94 years of age; females: 52.35 ± 17.38 years of age), with a male to female ratio of 1.09. The incidence of GPA was 0.37 per million patient-years (95% Poisson rate confidence interval 0.30–0.45). The incidence between 2003 and 2008 was higher than that reported between 1997 and 2002 (Table 2). ESRD occurred in two patients prior to and in four patients after the diagnosis of GPA. The time to ESRD after the diagnosis of GPA ranged from 10 months to 46 months.

Patient characteristics and clinical manifestations in the hospital-based study

Between October 2003 and October 2011, a total of 24 patients with AAV were classified based on the EMEA algorithm (Fig. 1), including eight patients with GPA, 14 patients with MPA, and two individuals with CSS. For diagnosis, sinus biopsy was performed in four out of eight patients with GPA, renal biopsy in one out of eight patients with GPA and in four out of 14 patients with MPA, and skin biopsy in one patient with GPA, two individuals with MPA, and one individual with CSS.

The initial presentation of eight patients with GPA was as follows: seven patients with sinusitis, two patients with hematuria, one individual with cranial neuropathy, and one individual with episcleritis. In a total of 14 patients with MPA, six patients had hemoptysis or pulmonary hemorrhage, nine patients had hematuria, and two individuals had neuropathy. Three patients had a cerebrovascular accident prior to a diagnosis of MPA. Additional clinical features are summarized in Table 3. Patients with MPA were older than those with GPA and CSS. PR3-ANCA was more prevalent in GPA, whereas MPO-ANCA was more prevalent in MPA. Both patients with CSS were ANCA negative.

As part of the treatment regimen, corticosteroids were used in 19 out of 24 patients with AAV. Cyclophosphamide was given in about half of patients (6 out of 8 patients with GPA, 5 out of 14 patients with MPA, and 2 out of 2 patients with CSS). Plasma exchange was performed in three patients with MPA; two individuals died (1 due to sepsis and 1 due to pulmonary hemorrhage) despite the plasma exchange, and the remaining one progressed to ESRD. Glucocorticoid and cyclophosphamide were used in two patients with CSS for skin papules and persistent sinusitis.

Pulmonary involvement was revealed by chest roentgenography or computed tomography in seven out of eight patients with GPA and in 11 out of 14 patients with MPA. Pulmonary hemorrhage was present in three out of eight patients with GPA and in seven out of 14 patients with MPA. Asthma developed 2 years prior to the diagnosis of CSS in the two patients.

At diagnosis, the median (range) serum creatinine level was higher in patients with MPA [3.1 (0.7–8.4) mg/dL] compared to patients with GPA [1 (0.7–1.8) mg/dL]. As a part of the study follow-up, kidney involvement (e.g., hematuria, proteinuria, or elevated creatinine) was found in all patients with MPA and in two out of eight patients with GPA. ESRD occurred in eight out of 14 of patients with MPA at diagnosis, and long-term renal replacement therapy was required in four of the nine survivors. One patient with GPA

Table 1 Age and sex distribution of GPA in Taiwan, 1997–2008

Age (y)	Male	Female	Total
<20	1	4	5
21–30	9	1	10
31–40	5	6	11
41–50	9	6	15
51–60	17	13	30
61–70	5	10	15
71–80	4	6	10
All	50	46	96

GPA = granulomatosis with polyangiitis.

Table 2 Incidence of GPA (per million patient-years) in Taiwan, 1997–2008

Years	Cases	Incidence	95% CI
1997–1999	17	0.27	0.16–0.44
2000–2002	14	0.22	0.12–0.36
2003–2005	34	0.51	0.35–0.72
2006–2008	31	0.46	0.31–0.65
All	96	0.37	0.30–0.45

GPA = granulomatosis with polyangiitis; 95% CI = 95% Poisson rate confidence interval.

Table 3 Clinical manifestations of patients with ANCA-associated vasculitis

	GPA (n = 8)	MPA (n = 14)	CSS (n = 2)
Age	50.9 ± 17.6	57.4 ± 17.8	43
Sex (M:F)	6:2	6:8	1:1
Anti-PR3	5 (62.5)	5 (35.7)	0 (0)
Anti-MPO	3 (37.5)	11 (78.6)	0 (0)
Clinical manifestations			
Lung involvement	7 (87.5)	11 (78.6)	2 (100)
ESRD	1 (12.5)	8 (57.1)	0 (0)
Neuropathy	2 (25)	3 (21)	2 (100)
Mortality	1 (12.5)	5 (35.7)	0 (0)
Treatment			
Glucocorticoid	8 (100)	9 (64.2)	2 (100)
Cyclophosphamide	6 (75)	5 (35.7)	2 (100)
Plasma exchange	0 (0)	3 (21.4)	0 (0)

Data are presented as n (%) or mean ± SD, unless otherwise specified.
ANCA = antineutrophil cytoplasmic antibody; CSS = Churg–Strauss syndrome; ESRD = end-stage renal disease; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; PR3 = proteinase 3.

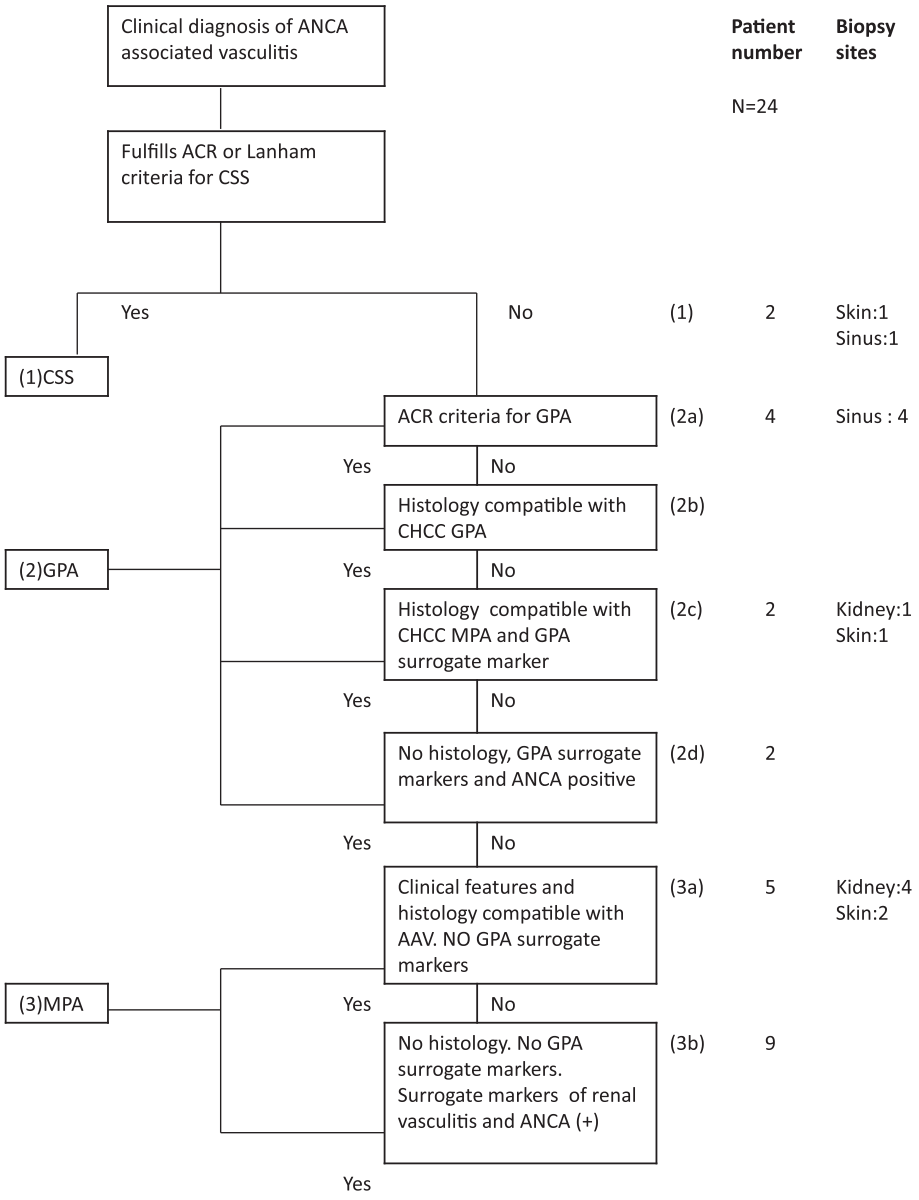

Figure 1. Classification algorithm. AAV = ANCA associated vasculitis; ACR = American College of Rheumatology; ANCA = antineutrophil cytoplasmic antibody; CHCC = Chapel Hill Consensus Conference; CSS = Churg—Strauss syndrome; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis.

progressed to ESRD within 3 months after diagnosis. No renal failure was noted in our patients with CSS.

Five out of the 14 patients with MPA died (2 from pulmonary hemorrhage, 2 from sepsis, and 1 from intracranial hemorrhage during sepsis). Among the eight patients with GPA, one died due to acute coronary syndrome. In the six patients with AAV who died, the median (range) interval to time of death post diagnosis was 26.5 (2—67) days. No deaths occurred in two patients with CSS, despite intracranial hemorrhage reported in one patient.

Discussion

In our study, the annual incidence of GPA was 0.37 per million between 1997 and 2008, according to the NHI database. In Hong Kong, the annual incidence of GPA has been estimated to be <2 per million.[10] Therefore, the incidence of GPA in the Chinese Han population is much lower than that observed in a Caucasian population.[4] However, the incidence of GPA varies greatly, even in a Caucasian population. For example, the incidence of GPA in Vilnius (the capital city), Lithuania, is 2 per million,[11] which is less than that observed in other European cities.[4] The observed incidence may change due to the availability of serologic tests and the awareness of treating physicians. Nevertheless, the currently available NHI data included 12 years of records, and we believe that the reported incidence of GPA is the best available description of incidence rates in a Chinese Han population.

Another important issue is whether the north—south gradient observed for the GPA/MPA incidence ratio exists in

populations other than a Caucasian population. According to the European data, the GPA/MPA incidence ratio is elevated in northern Europe compared with that in southern Europe.[4] Our data may provide an opportunity to examine this hypothesis further in a non-Caucasian population. According to studies in a Chinese Han population, the GPA to MPA ratio can range from 0.17 in a nephrologist-initiated study[12] to 0.66 in a rheumatologist-initiated study[13] (Table 4). A recent study in Beijing (latitude 39.9°N) that applied the EMEA algorithm revealed a GPA to MPA ratio of roughly 0.60[14]—which is similar to our study in New Taipei City (ratio 0.57; latitude 25.01°N). However, previous studies did not specify whether the reported cases were diagnosed newly or whether those relative frequencies were representative of the relative prevalence of AAV. Based on the currently available data, the issue of north—south gradient remains unresolved in Chinese Han societies.

A previous study in China showed that MPO-ANCA is more prevalent in patients with GPA,[14] whereas another study showed a greater prevalence of PR3-ANCA.[12] In the current study, the patients with GPA demonstrated an increased prevalence of PR3-ANCA. Another study of GPA patients in Taiwan revealed a predominant cytoplasmic ANCA pattern, which has been demonstrated to be associated strongly with PR3-ANCA.[6] Taken together, these results suggest similarities in the pattern of ANCA serology of GPA in a Taiwanese population compared with a Caucasian population.

MPA is more prevalent in Asia and seemed to be associated with higher mortality. MPA resulted in death in five out of 14 (35.7%) patients in the current study, which is closer to the proportion reported by Chen et al[12] [20 out of 84 patients with MPA (24%), with renal limited glomerulonephritis reclassified as MPA], but higher than that observed in a Caucasian population (0—23%).[15] In the current study, ESRD requiring long-term dialysis occurred in four out of the nine survivors. Mortality associated with GPA (12.5%) was not as high as that of MPA in our series. However, in a single-center study of GPA between 1985 and 2005 in Taiwan, a high mortality rate approaching 50% was reported.[6] As reported by Chen et al,[12] six out of 14 patients with GPA died (43%); half of these cases can be attributed to infection.

In our study, the relative frequency of CSS in AAV is similar to that reported by Zhang et al[13] (Table 4). In Taiwan, CSS is rare and only a few CSS case reports are available.[16—19] Most of these cases presented with more severe manifestations such as intracranial hemorrhage and multiple gastrointestinal ulcers, which was probably due to publication bias. However, one of our patients suffered from intracranial hemorrhage, demonstrating that CSS may be associated with significant morbidity.

Limitations to the current study are as follows. First, the incidence rates derived from the NHI database may be flawed due to incomplete coding or misclassification. It is not with absolute certainty that the ESRD cases in the database study can be attributed solely to GPA. Second, our clinical AAV series was small and represented only a single-center experience. Outcomes such as mortality or ESRD should be interpreted carefully due to a relatively short follow-up time.

In conclusion, our study provides a population-based estimate of the incidence of GPA in Taiwan. We also provide a hospital-based estimate of the relative frequency of AAV. All cases were diagnosed newly, which provided a good estimate of the relative incidence of AAV. Although biopsies were not performed in all patients, the use of a standardized EMEA algorithm provided a reliable classification for comparison with previously published studies. The geo-epidemiology information may help illuminate the interaction between ethnic background and environment in autoimmune diseases like AAV.

Table 4 Relative frequency of GPA, MPA, and CSS in hospital-based studies in Chinese Han societies

	Total cases	GPA	MPA	CSS	GPA/MPA
Hung et al,[7] Taipei[a]	18	4 (22.2)	14 (77.8)	0 (0)	0.29
Liu et al,[14] Beijing[b]	530	199 (37.5)	329 (62.1)	2 (0.4)	0.60
Chen et al,[12] Shanghai[a]	101	14 (13.9)	84 (83.2)	3 (2.9)	0.17
Zhang et al,[13] Beijing	179	61 (34.0)	93 (52.0)	25 (14.0)	0.66
This study	24	8 (33.3)	14 (58.3)	2 (8.3)	0.57

[a] Renal limited vasculitis was reclassified as MPA according to the EMEA algorithm.
[b] Excluding unclassifiable patients.
Data are presented as *n* (%).
CSS = Churg—Strauss syndrome; EMEA = European Medicines Agency; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis.

Conflicts of interest

All authors declare no conflicts of interest.

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